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07/975750

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(12) **United States Patent**
Ullrich et al.

(10) Patent No.: **US 6,177,401 B1**
(45) Date of Patent: **Jan. 23, 2001**

(54) **USE OF ORGANIC COMPOUNDS FOR THE INHIBITION OF FLK-1 MEDIATED VASCULOGENESIS AND ANGIOGENESIS**

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(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

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(22) Filed: **Feb. 9, 1994**

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(63) Continuation-in-part of application No. 08/038,596, filed on Mar. 26, 1993, now abandoned, which is a continuation-in-part of application No. 07/975,750, filed on Nov. 13, 1992, now abandoned.

(51) Int. Cl.⁷ **A61K 31/00**

(52) U.S. Cl. **514/1; 435/7.2; 436/501; 530/350; 530/399**

(58) Field of Search **536/23.5; 435/69.1, 435/172.1, 240.2, 252.3, 320.1, 325, 361, 7.2; 424/93.2; 514/44, 1; 935/32, 57, 70, 71; 436/501; 530/399, 350**

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,185,438 2/1993 Lemishka .
5,712,395 1/1998 App et al. .
5,763,441 6/1998 App et al. .
5,766,860 6/1998 Terman et al. .
5,792,771 8/1998 App et al. .
5,792,783 8/1998 Tang et al. .
5,869,742 2/1999 Köster et al. .

FOREIGN PATENT DOCUMENTS

WO 92/03459 3/1992 (WO) .
WO 92/14748 9/1992 (WO) .
WO 92/17486 10/1992 (WO) .
WO 94/10202 5/1994 (WO) .
WO 95/21868 8/1995 (WO) .
WO 96/20403 7/1996 (WO) .

OTHER PUBLICATIONS

S.H. Orkin Et Al., "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy", Dec. 7, 1995.*

H. Ueno et al., Science 252:844-848, May 10, 1991.*

H. Ueno et al., J. Biol. Chem. 267(3):1470-1476, Jan. 25, 1992.*

L.A. Tartaglia et al., J. Biol. Chem. 267(7), 4304-4307, Mar. 5, 1992.*

Risau et al., 1988, "Changes in the Vascular Extracellular Matrix During Embryonic Vasculogenesis and Angiogenesis," *Development Biology* 125:441-450.

Ferrara et al., 1989, "Pituitary Follicular Cells Secrete a Novel Heparin-Binding Growth Factor Specific for Vascular Endothelial Cells," *Biochem. Biophys. Res. Comm.* 161:851-858.

Gospodarowicz et al., 1989, "Isolation and Characterization of a Vascular Endothelial Cell Mitogen Produced by Pituitary-Derived Folliculo Stellate Cells," *Proc. Natl. Acad. Sci. USA* 86:7311-7315.

Leung et al., 1989, "Vascular Endothelial Growth Factor Is a Secreted Angiogenic Mitogen," *Science* 246:1306-1309.

Conn et al., 1990, "Purification of a Glycoprotein Vascular Endothelial Cell Mitogen From a Rat Glioma-derived Cell Line," *Proc. Natl. Acad. Sci. USA* 87:1323-1327.

Ullrich et al., 1990, "Signal transduction by receptors with tyrosine kinase activity", *Cell* 61:203-212.

Ferrara et al., 1991, "The Vascular Endothelial Growth Factor Family of Polypeptides," *J. Cell Biochem.* 47:211-218.

Kashles et al., 1991, "A Dominant Negative Mutation Suppresses the Function of Normal Epidermal Growth Factor Receptors by Heterodimerization," *Mol. Cell. Biol.* 11:1454-1463.

Klagsburn et al., 1991, "Regulators of Angiogenesis" *Annu. Rev. Physiol.* 53:217-39.

Maglione et al., 1991, "Isolation of Human Placental cDNA Coding For a Protein Related to the Vascular Permeability Factor," *Proc. Natl. Acad. Sci. USA* 88:9267-9271.

Matthews et al., 1991, "A Receptor Tyrosine Kinase cDNA Isolated From a Population of Enriched Primitive Hematopoietic Cells and Exhibiting Close Genetic Linkage to c-kit," *Proc. Natl. Acad. Sci. USA* 88:9026-9030.

Mitchell et al., 1991, "Recombinant Expression and Characterization of the 121 Amino Acid Form of Vascular Endothelial Growth Factor (VEGF)," *J. Cell. Biochem., Keystone Symposia on Molecular and Cellular Biology, Supplement 15C, Excerpt G207.*

(List continued on next page.)

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(57) **ABSTRACT**

The present invention relates to the use of proteins, peptides and organic molecules capable of modulating Flk-1 receptor signal transduction in order to inhibit or promote angiogenesis and vasculogenesis. The invention is based, in part, on the demonstration that Flk-1 tyrosine kinase receptor expression is associated with endothelial cells and the identification of vascular endothelial growth factor (VEGF) as the high affinity ligand of Flk-1. These results indicate a major role for Flk-1 in the signaling system during vasculogenesis and angiogenesis. Engineering of host cells that express Flk-1 and the uses of expressed Flk-1 to evaluate and screen for drugs and analogs of VEGF involved in Flk-1 modulation by either agonist or antagonist activities is described.

The invention also relates to the use of FLK-1 ligands, including VEGF agonists and antagonists, in the treatment of disorders, including cancer, by modulating vasculogenesis and angiogenesis.

16 Claims, 25 Drawing Sheets